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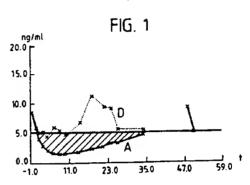
(54) Bromocriptine compositions

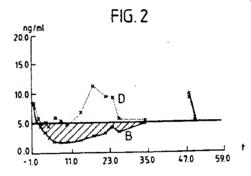
(57) Oral controlled release formulations comprise bromocriptine, a hydrophilic swelling substance and an inert fatty material.

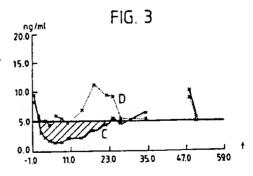
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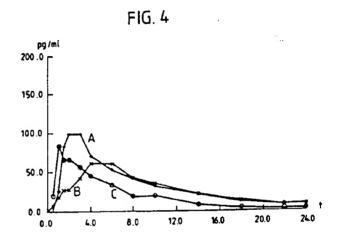
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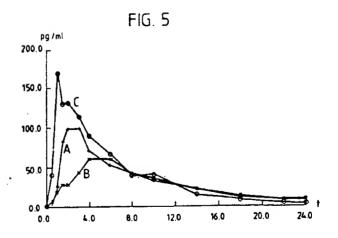
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## SPECIFICATION

## **Bromocriptine compositions**

	Bromocriptine compositions	
5	5 This invention relates to pharmaceutical compositions, containing bromocriptine. Bromocriptine is the generic name for the compound 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'α-(2-methylpropyl)ergotamin-3',6-tri-one and is listed in the Merck Index, 1976, Appendix A 2.	5
10	Bromocriptine is a well-known dopamine agonist used in the treatment of e.g. hyperprolactine mia, acromegaly and Parkinson's disease. It is usually administered in the form of the mesylate in daily dosages of e.g. 5-7.5 mg, 10-60 mg and 20-80 mg respectively. Its pharmacological and clinical properties have been recently extensively reviewed in M.O. Thorner et al.: Bromocriptine A clinical and pharmacological review, Raven Press, New York 1980. However	10
15	the pharmacokinetic profile was not been established conclusively. From extensive pharmacokinetic studies we have found that bromocriptine is rapidly absorbed and rapidly eliminated from plasma after oral administration (t $1/2 = 3$ to 5 hours). Although its duration of action appears to extend well beyond t $1/2$ in some applications (e.g hypoprolactinaemia effect), we have	15
20	found that it is generally necessary to administer the daily doses in 2 to 4 small doses to achieve a lasting therapy and to decrease potential unwanted side effects, which are thought to be related to the rapid absorption of the drug. Some of these side effects are due to dopaminergic activity of the compound acting on dopaminergic receptors in the gastro-intestinal tract, e.g. nausea and emesis.	20
25	There exists thus a need for a controlled release formulation of bromocriptine which provides a prolonged action of bromocriptine to reduce the number of times bromocriptine has to be administered each day and to reduce certain adverse reactions.  The present invention provides a controlled release formulation for oral administration	25
	comprising bromocriptine a pharmaceutically acceptable hydrophilic swelling substance and a pharmaceutically accept-	
30	able inert fatty material.  The preferred amounts of bromocriptine in the unit dosage form are from 2 to 20 mg, especially 5 and 10 mg. The bromocriptine may be in free base form or in the form of a pharmaceutically acceptable acid addition salt. Preferably the bromocriptine is in mesylate salt	30
35	form. Reference herein to bromocriptine is intended both the free base form and such salts forms.  Hydrophilic swelling substances that can be used include one or more natural, partially or totally synthetic anionic or, preferably, nonionic hydrophilic gums, modified cellulosic sub-	35
40	stances or proteinaceous substances such as, for example, acacia, gum tragacanth, locust bean gum, guar gum, karaya gum, agar, pectin, carrageen, soluble and insoluble alginates, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxypethylcellulose, sodiumcarboxymethylcellulose, carboxypolymethylene, gelatin.  Preferred are cellulose hydrocolloids which include methyl cellulose, hydroxypropylcellulose	40
45	and especially hydroxypropylmethylcellulose and sodium carboxymethylcellulose. Preferably the weight ratio of bromocriptine to the hydrophilic swelling substance is from 1:10 to 1:35, especially from 1:16 to 1:25.  The weight ratios refer to the amount of active substance bromocriptine, not the total weight	45
50	of any salt.  Usable phermaceutically acceptable inert fatty materials include beeswax; fatty acids; long chain fatty alcohols such as, for example, cetyl alcohol, myristyl alcohol, stearyl alcohol, glycerides such as glyceryl esters of fatty acids or hydrogenated aliphatic acids such as, for example, glyceryl monostearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and the like, oils such as mineral oil and the like. Fatty materials are preferably such with	50
55	melting points between 30 and 90°C.  Most preferred fatty materials have a melting point from 45°C to 65°C and include glycerides such as glyceryl palmitates and stearates and fatty acids such as hydrogenated castor oil and fatty acid esters such as cetyl palmitate. Preferably the weight ratio of bromocriptine to the fatty	<b>5</b> 5
60	material is from 1:1 to 1:10, especially from 1:6 to 1:10. It is also convenient to incorporate in the formulation other soluble or insoluble pharmaceutical excipients such as calcium sulfate, calcium phosphate, factors and collorat silica. The weight ratio of bromocriptine to these other excipients is conveniently from 1:5 to 1:40, e.g. 1:15 to 1:40.	60
	The formulation may be produced in conventional manner by mixing the ingredients together, if desired melting the fatty material. The resultant mixture is in powder form. The powder can be	

5	fact that bromocriptine is sensitive to many chemical reagents. Moreover, the formulation a satisfactory pharmacodynamic and pharmacokinetic profile.  The resultant retarded formulations in general have comparable bio-availability in statinical trials to conventional non-retarded formulations containing the same amount of criptine. The formulations of the invention, even if administered once a day, can still profit therapeutic effect for at least 24 hours and even as much as 35 hours. The formulation therapeutic effect for at least 24 hours and even as much as 35 hours. The formulation that are the same proposed in the conventional non-retarded forms.	bromo- roduce a 5 n may
10	thus be administered only once a day in the known indications on retarded forms, mately the same daily doses as employed in the conventional non-retarded forms. Preferred formulations such, which shown in vitro release experiments a release to bromocriptine of less than 50% in 2,5 hours, preferably a release rate of less than 65° bromocriptine of less than 50% in 2,5 hours, preferably, the formulation will release hours, as measured in 0,1 n HCl solution. Most preferably, the formulation will release	ate of % in 8 10
15	80% of the active ingredient within the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples all temperatures are in degrees Centigrade and are uncorrunted in the following examples and are uncorrunted in the following examples are uncorrunted in the following examples and are uncorrunted in the following examples are uncorrunted in the f	ereinafter or other 15
20	zende Gebiete. 2nd Edition 1997; Silica is e.g. brand Aerosil 200 available from Deutsche-Gold und Siberscheidanstal Silica is e.g. brand Aerosil 200 available from Deutsche-Gold und Siberscheidanstal Frankfurt, W. Germany.	sse 20
25	929100 Voulogne-Brillancourt, France. 929100 Voulogne-Brillancourt, France. Hydroxypropylmethylcellulose 15000 cps and 4000 cps are e.g. brands Methocel Hydroxypropylmethylcellulose 15000 cps and 4000 cps are e.g. brands Methocel E4M available from Dow Chemical Company, Michigan 48640 USA. Methocel E4M available from Dow Chemical Company, Michigan 48640 USA. Cetyl palmitate is e.g. brand Cutina CP available from Henkel 4000, Düsseldorf, W	Germany.
2.0	EXAMPLE 1: Composition of each capsule	
30	Ingredient mg  1) Bromocriptine mesylate 5.735 *)  124.265  30 2) Lactose (200 mesh) 10  3) Silica 40  4) Glycerol ditripalmitostearate 4000 cps 110	30
_	5) Hydroxypropylmethylcellulose 4000 cps 290	35
3	35 Capsule (Hard gelatine) 78	
4	*)equivalent to 5 mg bromocriptine base	40 to 56°C
	Ingredients 1). 2) and 3) are sieved and mixed. Ingredient 4) is fielded by Ingredients 1). 2) and 3) are sieved and mixed. Ingredient 4) is fielded by Ingredient 5 is stirret (m.p. 54°C) and is added to the mixture which is heated to 55°C. The mass is stirret (m.p. 54°C) and is added to the mixture and cooled overnight. The crushed mass minutes or until it is a homogenous mixture and cooled overnight. The crushed mass up and sieved (through 250 micron openings). Ingredient 5) is sieved (through 360 up and sieved (through 250 micron openings). The mixture is then encapsulated.	s is proken
	In vitro release Gastric juice 0.1 n HCI (pH 1.2)	50
5	50 Time Release of bromocriptine (hours)	30
•	1 7% 2 13% 4 28% 55 6 42% 24 100%	55

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_	EXA	AMPLE 2: Composition of each capsule			
5	1) 2) 3)	Ingredient Bromocriptine mesylate Calcium sulfate . 2H <sub>2</sub> O	mg 5.735 124.265 20.0	<b>)</b>	5
10	4)	Hydroxypropylmethylcellulose (15000 cps)  Capsule (hard gelatine)	270.0 78.0	_	10
	*)eq	uivalent to 5 mg bromocriptine base		·	
15	folio	paration Inalogous to Example 1, with the difference, owed by addition of ingredient 3) in molten tredient 4) is added.	that now ig form, after v	redients 1) and 2) are mixed, which the mixture is cooled and	15
••		AMPLE 3: Composition of each capsule			20
20	1} 2)	Ingredient Bromocriptine mesylate Maleic acid	11.47		
25	3) 4) 5)	Lactose Silica Cetyl palmitate	78.53 10.00 40.00		25
	6)	Hydroxypropylmethylcellulose 15.000 cps	130.00	_	
30		Capsule (hard gelatine)	274.00 81.00	_	30
35	Pre A foll	orresponding to 10 mg bromocriptine base sparation Analogous to Example 1, with the different th owed by addition of ingredient 5) in molten redient 6) is added.	at now ingr form, after v	edients 1), 2), 3) and 4) are mixed, which the mixture is cooled and	35
40		mparative clinical tests Objectives: To study in healthy volunteers the opression effects of two oral controlled releas opparison to a conventional capsule C and a p	e capsules A	A and B according to the invention in	40
45	A.	Composition according to the invention			45
50	1. 2. 3. 4.	Glycerol-ditripalmito stearate	mg 5.735 184.265 20.000 60.000	"	50
55	1	orresponding to 5 mg bromocriptine The fatty acid component A3, was added in r , and mixed therewith after which the mixtur imponent A4, was mixed with the mixture of	e was coole	d to room temperature and	55

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В.	Composition according to the invention			
	Ingredient	mg		5
5 1.		5.735		•
5 1. 2.		124.265		
2	Silica	10.000		
4	or chancel distingimito stearate	40.000		
5.		110.000		10
10			- A with the excention that instead	
	The mixture was prepared analogous to the n	nixture uno	er A, With the exception the	
of	mixing A1. and A2., B1., B2. and B3. were	mixed.		
				15
4.5				15
15	Ingredient	mg	•	
1.	- '	2.87	*)	
2.		2.00		
3		170.63		20
20 4		120.00		
5	·	1.50		
6		3.00		
74				
7)	corresponding to 2,5 mg bromocriptine			25
25	The ingredients 1 to 6 were mixed together			
D	) Conventional placebo composition			
_		mg		30
30	Ingredient	190.00		
1	Lactose	20.00		
	Glycerol ditripalmito stearate Hydroxypropylmethylcellulose (4000 cps)		•	
3	Hydroxypropylmethylicellalose (4000 cps)		man and missed thoroughth	35
35 .	The fatty component D2 was added in molte	en form to (	component D1 and mixed therewith.	-
,,,	The fatty component D2 was added in molte the mixture was cooled to room te	mperature a	and mixed with component bo.	
	Instead of 5 mg bromocriptine, as present in	n capsule A	and B, the horizotta capacita	
	Instead of 5 mg bromocriptine, as present it ontained only 2.5 mg bromocriptine to avoid	a too stron	g influence on the healthy volumests	
	by expected side effects.		consisted at 8.00 h in the	40
40	by expected side effects.  In a randomized double-blind design 8 heal	thy male vo	lunteers received at 5.00 if in the	
40	In a randomized double-blind design 8 hear norning either one capsule A, B, C or D in su	ch a manne	that each volunteer received the	
Ċ	norning either one capsule A, B, C or D in su different capsule types, divided over 4 admini	stration day	s, separated by an interval of a meaning	
			•	
1	Prolactin inhibition  Blood samples were obtained from the 8 vo	dunteers by	an indwelling cannula, in certain time	45
45	Blood samples were obtained from the 8 volume and 8.00 h, the time the capsule with the same and the same transition from 18	as received	till 10.00 h on the third day (totally	
į	ntervals from 8.00 h, the time the capsule was 50 hours); with a longer interruption from 18	00 till 8.0	) h in the second night. The prolactin	
!	50 hours); with a longer interruption rolling levels were determined by a specific radioimm	nunnassav.		
I	evels were determined by a specific radioinm The prolactin concentrations, measured after	r the admir	istration of capsules A, B and C were	
	The prolactin concentrations, measured are plotted graphically as corresponding mean cu	rves A (Fig.	1), B (Fig. 2) and C (Fig. 3).	50
50 (	plotted graphically as corresponding mean cu The prolactin concentrations, determined at	ter the adm	inistration of capsule D, were depicted	
	The prolactin concentrations, determined at as curve D in Fig. 1, 2 and 3, which was con	pared with	curves A, B and C (in nanograms/ml,	
	as curve D in Fig. 1, 2 and 5, which the	•		
	time t in hours).  The prolactin curve D represents the norma	I prolactin o	concentration of healthy volunteers	
	The projectin coive b represents the	•		55
55	during night and day. In the evening, the concentration rises, dur	ing sleep th	e maximum is reached and in the tirst	
	In the evening, the concentration rises, dur wakening hours the concentration falls to a d	av-time "ba	sal level" which is maintained to about	
	the corresponding capsules A and B and lasti	ng 35 hour	\$.	
	the corresponding capsules A and B and lasti Capsule C produces a protactin inhibition in	healthy vo	lunteers, 1 hour after taking a capsule	60
60	Capsule C produces a production			
	C and lasting only 24 hours.			

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4 (in picograms/ml, time t in hours).

The concentrations of curve C in Fig. 4, caused by the 2.5 mg bromocriptine containing capsule C were doubled and plotted in Fig. 5 as a curve C adapted to a double portion of capsule C, together with curves A and B, so that bromocriptine levels of equal dosages of 5 bromocriptine (5 mg) can be compared.

From Fig. 5 it is seen that the rate at which drug concentrations initially rise (i.e. absorption phase) is slightly reduced for form A and markedly reduced for form B as compared with twice

It also appears from these mean curves, that bioavailabilities (AUC\*) of capsules A and B are 10 somewhat lower than of two capsules C.

\*Area under curve

Based on the individual subjects data, the reduction in bioavailability was an average of 12% 15 for form A and 25% for form B.

Tolerability

The side effects experienced by each volunteer were recorded as to type, duration and intensity (strong, moderate and weak). Overall the following side effects were noted:-

0				
_	1)	orthostatic hypotonia	8)	head pressure
•	21	dizziness	9)	drowsiness
	31	vomiting	10)	tiredness
	41	nausea	111	weakness
_		concertion	121	sweating

heat sensation 6) headache 14) abdominal cramps 7) dry mouth palor

side effects 1) to 6) are well known for dopamine agonist drugs like Bromocriptine and were used to assess the relative tolerability of the formulations in the table below:

number of drug related side effects						
Intensity	A 5 mg drug	B 5 mg drug	C 2.5 mg drug	D placebo		
strong	10	5	1	1		
moderate	16	9	1	0		
weak	12	5	11	3		
total	38	19	13	4		
	strong moderate weak	Intensity A 5 mg drug  strong 10 moderate 16 weak 12	Intensity  A B 5 mg drug 5 mg drug  strong 10 5 moderate 16 9 weak 12 5	Intensity         A 5 mg drug         B 5 mg drug         C 2.5 mg drug           strong         10         5         1 moderate           moderate         16         9         1 moderate           weak         12         5         11		

Capsule A produces significantly more drug related side effects than all other forms. Capsule B produced fewer drug related side effects than A, and the total number was not statistically different from the 2.5 mg conventional form C.

Capsule C produced significantly more drug related side effects than placebo D. On the basis of tolerability, Capsule B is to be preferred over capsule A

In in vitro experiments (USP XXI, page 1243-1244, Apparatus 1, 1000 ml 0.1 n HCl, 100 55 rotations per min.) the following release results were obtained with capsules A, B and C:-

		of weights)				
		Capsule A	Capsule B	Capsule C		-5
5	0,5	13	4	99		
	1	23	8	100		
	2	42	15 28			10
	4	66 81	39			10
	6	89	48			
	8 10	94	57			
	14	98	68			
	24	100	86			15
,	From the viewpoint of preferred and capsule	of pharmacoking	netics capsules preferred.	A and B are		
				and cimultaneou	sly, would not be tolerated	20
ì	A daily dosage of tv	vo capsules of	C. if administe	red simultaileou	317, 1102-12	
	Both capsules A and	d B, if administ e bromocriptin ood, notwithsta capsule B is pre	tered once a di e concentration	y surprisingly C n for 24 hours a	ause a satisfactory nd a prolactin suppression availability in comparison ess side effects and its	25
	CLAIMS  1. A controlled rel	ease formulation	on for oral adm	inistration comp	rising	30
c	-bromocriptine		Jaanhilia ewalli	no substance		
	a abarmaceuticaily	acceptable ny	Tiobinic anom	g		
			er fatty materia	al.		
	a pharmaceutically	acceptable ine	rt fatty materia	il. ig 2 to 20 mg d	f bromocriptine per unit	
	<ol><li>A formulation a</li></ol>	acceptable inc	im 1 containir	īg 2 to 20 mg d	f bromocriptine per unit	3
•	2. A formulation a dosage form.	according to cla	aim 1 containir aim 2 containir	ng 5 mg bromot	riptine.	3
	2. A formulation a dosage form.	according to cla	aim 1 containir aim 2 containir	ng 5 mg bromot	riptine.	3
•	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a	acceptable inc according to cla according to cla according to ar	aim 1 containing aim 2 containing aim 2 containing one of the p	ng 2 to 20 mg o ng 5 mg bromot ng 10 mg bromot receding claims	riptine. periptine. wherein the swelling	3
	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a	acceptable inc according to cla according to cla according to ar	aim 1 containing aim 2 containing aim 2 containing one of the p	ng 2 to 20 mg o ng 5 mg bromot ng 10 mg bromot receding claims	riptine. periptine. wherein the swelling	
	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a substance is a cellulo	acceptable indiccording to classics of classics according to classics according to an	aim 1 containing aim 2 containing aim 2 containing one of the plant of the plant one of the plant of t	ng 2 to 20 mg cong 5 mg bromotog 10 mg bromotog telegraphics claims receding claims	riptine. ocriptine. wherein the swelling wherein the swelling	
	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a substance is a cellulo 6. A formulation a substance is hydroxyl 2. A formulation	according to cla according to cla according to cla according to ar se hydrocollog according to ar propylmethylce according to ar	aim 1 containing aim 2 containing aim 2 containing yone of the plan one of the plan of the pla	ng 2 to 20 mg of mg 5 mg bromotor of 10 mg bromotor receding claims receding claims	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of	
	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a substance is a cellulo 6. A formulation a substance is hydroxyl 2. A formulation	according to cla according to cla according to cla according to ar se hydrocollog according to ar propylmethylce according to ar	aim 1 containing aim 2 containing aim 2 containing yone of the plan one of the plan of the pla	ng 2 to 20 mg of mg 5 mg bromotor of 10 mg bromotor receding claims receding claims	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of	
	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a substance is a cellulo 6. A formulation substance is hydroxy 7. A formulation bromocriptine to the 9. A formulation	according to cla according to cla according to all according to all according to are propylmethylee according to all according to all according to all	aim 1 containing aim 2 containing aim 2 containing aim 2 containing and a containing aim of the poly one of the pance is from 1 and one of the pance is from 1 and one of the pance aim of	ng 2 to 20 mg of mg 5 mg bromot ng 10 mg bromot receding claims receding claims to 1:35.	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of wherein the weight ratio of	4
	2. A formulation a dosage form. 3. A formulation a 4. A formulation a 5. A formulation a substance is a cellulo 6. A formulation o substance is hydroxyl 7. A formulation bromocriptine to the 8. A formulation the swelling substance	according to cla according to cla according to an according to an according to an according to an propylmethylce according to an according to an according to an according to an	aim 1 containing aim 2 containing aim 2 containing aim 2 containing appropriate properties of the properties of the properties of the properties from 1 appropriate aim from 1 appropri	ng 2 to 20 mg of mg 5 mg bromong 10 mg bromong claims receding claims to 1:35.  The control of the control of the control of 1:35.  The control of the contr	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of wherein the weight ratio of wherein the fatty acid	4
. (	dosage form.  3. A formulation of the following substance is a cellulo 6. A formulation of the following substance is hydroxy 7. A formulation bromocriptine to the 8. A formulation the swelling substance to the swelling substa	according to cla according to cla according to a according to a se hydrocolloid according to a propylmethylce according to a swelling substa according to a according to a	aim 1 containing aim 2 containing aim 2 containing aim 2 containing appropriate propriate propri	ng 2 to 20 mg of mg 5 mg bromoting 10 mg bromoting claims receding claims 10 to 1:35.  Treceding claims 16 to 1:25.  Treceding claims 16 to 1:25.  Treceding claims 16 to 1:25.	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of wherein the weight ratio of wherein the fatty acid	4
•	dosage form.  3. A formulation at 4. A formulation at 5. A formulation bromocriptine to the 8. A formulation at 6. A formulation material is a hydrophase of a formulation material at 6. A formulation material at 6. A formulation formulation formulation formulation formulation at 6. A formulation formu	according to cla according to cla according to are according to are se hydrocolloid according to are propylmethylce according to are according to are according to all according to all	aim 1 containing aim 2 containing one of the parce is from 1 any one of the parce is from 1 any one of the parting any one of the	ng 2 to 20 mg of a graph of the state of the	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of wherein the weight ratio of wherein the fatty acid O and 90°C. Is wherein the fatty material	4
. (	dosage form.  3. A formulation at 4. A formulation at 5. A formulation bromocriptine to the 8. A formulation at 6. A formulation material is a hydrophase of a formulation material at 6. A formulation material at 6. A formulation formulation formulation formulation formulation at 6. A formulation formu	according to cla according to cla according to are according to are se hydrocolloid according to are propylmethylce according to are according to are according to all according to all	aim 1 containing aim 2 containing one of the parce is from 1 any one of the parce is from 1 any one of the parting any one of the	ng 2 to 20 mg of a graph of the state of the	riptine. scriptine. wherein the swelling wherein the swelling wherein the weight ratio of wherein the weight ratio of wherein the fatty acid O and 90°C. Is wherein the fatty material	4
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	Balance of h	romocriptine (i	n percents		
Release time in hours	of weights)		Capsule C		_
	Capsule A	Capsule B			5
0,5	13	4 8	99 100		
1	23	15	100		
2	42	28		•	10
4	66	39			
6	81 89	48			
8	94	57			
10	98	68			
14	100	86			15
			A   B 050		
From the viewpoint	of pharmacokir	netics capsules	A and b are		
preferred and capsule	D to eshecient	F			
0			المعمداليم	sly, would not be tolerated	20
Summary.	wo capsules of	C, if administe	ited simultaneor	.,	
in clinical practice as i	reported before		aurorisinaly o	use a satisfactory	
			o for 24 hours a	nd a prolactin suppression invalidability in comparison	
					25
for 35 hours in the bl	ood, notwithsta	inding a silyani	cince it causes	ess side effects and its	2:
- Jahanna consilles L. I	Capsule D is P.	eterably used.	311100 11 00		
controlled absorption	is better.				
CLAIMS			interestion com	risina	_
CLAIMS  1. A controlled re	lease formulation	on for oral adm	imistration com		30
0 -bromocriptine		أألمس منات	na substance		
	acceptable by	orophilic swell	al	•.	
—a pharmaceutically —a pharmaceutically	acceptable inc	im 1 containi	no 2 to 20 mg (	f bromocriptine per unit	
2 Δ formulation :	accoloning to co		-		3
descent form.			E ma bromoi	rintine.	•
35 3 A formulation	according to ci	aim 2 containi	ng 10 mg brom preceding claims	criptine.	
4 A formulation	according to a	ov one of the p	receding claims	wherein the swelling	
5. A formulation	according to o	1		·	
substance is a cellulo	se nydroconon	ny one of the p	receding claims	wherein the swelling	4
6. A formulation	according to o	llulose.		the weight ratio of	
6. A formulation 40 substance is hydroxy	propymietry.o.	ny one of the p	preceding claims	wherein the weight ratio of	
7. A formulation bromocriptine to the	swelling subst	ance is from 1	:10 to 1:35	t the waight ratio of	
bromocriptine to the	according to 8	ny one of the I	preceding claims	wherein the weight ratio of	
8. A formulation the swelling substan	ce to bromocri	ptine is from 1	:16 to 1:25	wherein the fatty acid	4
				wherein the fatty acid 0 and 90°C.	
45 9. A formulation material is a hydropl	hobic material	with a melting	point between	s wherein the fatty material	
has a melting point	from 45 to 65	°C.	anding clair	s wherein the fatty material is	
11 A formulation	on according to	any one of the	s preceding elem		
50 a glyceride.		1.: 11 who	rain the alveerid	e is glycerol ditripalmitostear-	
12. A formulation	on according to	CISIM I I WILE	(Cil) tive g-7	is glycerol ditripalmitostear-	
ate.	-dimm to	any one of th	e preceding clair	ns wherein the weight ratio of	
13. A formulation bromocriptine to the	on according to	is from 1:1 to	1:10.		!
bromocriptine to the	e tatty material	claim 13 whe	rein the weight	atio is from 1.6 to 1.10.	
				atio is from 1:6 to 1:10.  ns containing hydroxypropylate as a fatty material.	
methylcellulose as	a sweming age	claim 15, cor	ntaining bromoc	iptine. hydroxypropylmethylcel- 1:22:8 or 1:12:4.	
	discipal mithetes	arate in a weigi	IN TALLO OF BOOK	t	
		ion of a contro	illed release form	ulation for oral administration, tance and a fattay material acromegaly, or Parkinson's	

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or Parkinson's disease according to the method of claim 18 in unit dosage form, containing 2 to 20 mg of bromocriptine. 20. A formulation according to claim 1 substantially as hereinbefore described with reference to any one of the Examples. 21. A controlled release formulation of bromocriptine releasing less than 50 percent by weight of bromocriptine within 2.5 hours as measured in 0,1 n HCl in in vitro release experiments.

22. A controlled release formulation according to claim 21 releasing less than 65 percent by weight within 8 hours.

23. A controlled release formulation according to claims 21 or 22 releasing at least 80 10

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percent by weight within 24 hours.